

Applicant : Richard F Selder et al.  
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### REMARKS

The specification has been amended to clarify the identity of the sequence at page 33, line 3 from the bottom, and to delete references to Genbank Accession Numbers.

Claim 15 has been canceled. Claims 16-25 are withdrawn from examination as being drawn to non-elected subject matter. Claims 1, 3, 4, 8 and 12 have been amended and claims 26-32 added. The amended and new claims are supported throughout the application as filed, e.g., at page 3, lines 17-19; page 4, lines 9-11 and 25-27; and pages 21-23. Claims 3, 4 and 8 have been amended merely for clarity. No new matter has been added.

Upon entry of this amendment, claims 1-14 and 16-32 will be pending. Claims 1-14 and 26-32 will be under examination.

### Sequence Listing

The Examiner states that "page 33, line 3 from the bottom, an amino acid sequence is not identified with a sequence identification number. Appropriate correction is required"

Applicants note that the "ARG" in the "X-ARG-X-X-ARG" sequence at page 33, line 3 from the bottom, stands for the single amino acid arginine (Arg), as shown, e.g., at page 8, line 16. To make this more clear, the specification has been amended at page 33 to recite the "X-Arg-X-X-Arg" sequence using the title case rather than uppercase abbreviation, making the disclosure of the sequence at page 33 consistent with that at page 8. Because this sequence has fewer than four specifically defined amino acids, a sequence identifier for this sequence is not required under 37 C.F.R. §1.821(a).

### Objections to the Specification

All references in the specification to Genbank Accession numbers have been deleted, thereby obviating the objection to the specification on that basis. Accordingly, Applicants respectfully request that the objections be withdrawn.

Rejections Under 35 U.S.C. 112, Second Paragraph

Claims 1-15 are rejected as allegedly indefinite in the recitation of "non-common," "less common" and "common" codon. The rejection has been addressed by amending claims 1 and 12 to specify the most common codon representing a particular amino acid in a human sequence, as defined in the specification. The specification provides definitions of "non-common," "less common" and "common" codons at page 21, as follows:

By "common codon" is meant the most common codon representing a particular amino acid in a human sequence. The codon frequency in highly expressed human genes is outlined below in Table 1. Common codons include: Ala (gcc); Arg (cgc); Asn (aac); Asp (gac); Cys (tgc); Gln (cag); Gly (ggc); His (cac); Ile (atc); Leu (ctg); Lys (aag); Pro (ccc); Phe (ttc); Ser (agc); Thr (acc); Tyr (tac); Glu (gag); and Val (gtg) (see Table 1). "Less-common codons" are codons that occurs frequently in humans but are not the common codon: Gly (ggg); Ile (att); Leu (ctc); Ser (tcc); Val (gtc); and Arg (agg). All codons other than common codons and less-common codons are "non-common codons".

Applicants submit the claims are quite clear in view of the above definitions provided in the specification. A common codon is "the most common codon representing a particular amino acid in a human sequence." Common codons include those listed as such in the passage above. The skilled artisan would understand that common codons also include atg (Met) and tgg (Trp), since these are the only codons for these two amino acids. Less-common codons are explicitly listed in the passage quoted above. Non-common codons are explicitly defined as all codons other than common and less-common codons. Thus, the Examiner's concern that the "non-common" vs. "less-common" codons are difficult to distinguish with regard to Lys, Cys, Gln, Glu, His, Thr and Phe, is groundless. In view of the definition quoted above, each of Lys, Cys, Gln, Glu, His, Thr and Phe has a common codon and non-common codons only (and no "less-common codons"). Accordingly, the claims are definite and Applicants respectfully request that the rejection be withdrawn.

Double Patenting

Claims 1-15 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as unpatentable over co-pending application 09/407,605 (which is the parent of the instant application). 09/407,605 and the instant application are

commonly owned. Applicants will address any double patenting rejection by filing a terminal disclaimer under 37 C.F.R. 1.321(c) or taking another appropriate action once the present claims are deemed otherwise allowable.

Rejections Under 35 U.S.C. §103

Claims 1-15 are rejected as unpatentable over Seed WO96/09378 (Seed) in view of Kim et al. 1997, *Gene* 199:293-301 (Kim); Morgan et al., 1987, *Pediatr. Nephrol.* 1:536-539 (Morgan); Bishop et al., 1986, *PNAS USA* 83:4859-63 (Bishop); and Wada et al., 1992, *Nucleic Acids Res.* 20:2111-18 (Wada). This rejection is respectfully traversed. To establish prima facie obviousness of a claimed invention, the prior art must teach or suggest the invention, and the motivation to arrive at the present invention and a reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). In this instance, a prima facie case of obviousness has not been made because the cited references, alone or in combination, fail to provide a teaching or motivation for a skilled artisan to arrive at the presently claimed synthetic nucleic acid sequences. In particular, the present claims are directed to synthetic  $\alpha$ -galactosidase nucleic acids (and related methods of making them) which have one or more of: a very long stretch of common codons (at least 150 continuous common codons); a stretch of common codons which is a very large percent of the total sequence (at least 60% of the total sequence is common codons); or a very high total percentage of common codons (at least 94% common codons). As discussed in detail below, the claimed  $\alpha$ -galactosidase nucleic acids are enriched with common codons to a very high extent not taught by the prior art. In fact, the art teaches away, and cautions one to not use the levels of codon replacement required by the present claims.

Seed provides only a generalized description of optimized nucleic acid sequences that neither teaches nor suggests synthetic sequences (much less  $\alpha$ -galactosidase sequences) with the specific range of common codons as presently claimed. Further, with regard to nucleic acids having a high proportion of common codons, Seed is at best, silent and at worst, dissuasive. In particular, Seed cautions that "[in] constructing the synthetic genes of the invention it may be desirable to avoid CpG sequences as these sequences may cause gene silencing." Because the common codons in human sequences are exceedingly CG rich, this statement alone would lead a

skilled artisan away from making the synthetic sequences as presently claimed, which have very high numbers of human common codons. Therefore, far from providing the required teaching or motivation, Seed teaches away from the present claims.

Kim does not add anything to the disclosure of Seed. If anything, Kim provides additional disincentives to make the claimed nucleic acids. Kim describes the replacement of native codons with yeast and human preferred codons, resulting in a hybrid gene. Kim et al. use preferred yeast codons because preferred yeast codons, unlike preferred human codons, are not as GC rich. Kim et al state:

Re-engineered genes with human codon usage become high in their GC content. Although a low GC content of 5' UTR is ensured, optimizing the re-engineered gene further by decreasing the GC content of the limited region downstream of the initiator codon is advisable. (Kim, page 299, last paragraph)

Thus, Kim et al. also teach away from the present invention by suggesting that a synthetic nucleic acid sequence should not have a high percentage of human common codons. Accordingly, the Examiner's statement that "the ordinary skill in the art would have been motivated to change every single less-common and non-common codon to a common codon to optimize the level of expression of the desired  $\alpha$ -galactosidase in the host cell so the resulting sequence could be 100% common codons" is clearly unsupported in view of the disclosures of Seed and Kim. In fact, a skilled person reading Seed or Kim would have believed that an  $\alpha$ -galactosidase sequence with all or almost all common codons would have reduced expression, because such a sequence would have a high GC content. Thus, the Examiner has provided no evidence of a motivation in the art to arrive at the present claims.

In contrast to the suggestions in Seed and Kim, Applicants have found that "systemic codon optimization (with disregard to CpG content) provides a fruitful strategy for improving the expression in mammalian cells of a wide variety of eukaryotic genes." (See page 47, lines 15-18 of Applicants' disclosure, emphasis added). Indeed, Applicants found that synthetic  $\alpha$ -galactosidase sequences containing the very large continuous stretches or overall very high numbers of common codons recited in the claims, resulted in 2.0- and 5.7-fold increases in mean  $\alpha$ -galactosidase expression compared to the wild-type sequence (see table 10 and accompanying discussion at page 72 of Applicants' disclosure). In view of the prior art's clear teaching away

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from sequences containing very high numbers of common codons, Applicants' results are indeed surprising.

With Seed and Kim teaching away from the present claims, the Examiner is left only with Morgan, Bishop and Wada to provide the motivation and reasonable expectation of success required for a *prima facie* case of obviousness. Morgan, Bishop and Wada, alone or in any combination, do not make up for the deficiencies of Seed and Kim, as none of these references discloses or suggests synthetic nucleotide sequences containing the high numbers of common codons as recited in the present claims. Therefore, none of the cited references, alone or in combination, provide a teaching or a motivation for a skilled artisan to arrive at the present claims. Accordingly, Applicants submit that the references do not support a *prima facie* case of obviousness under the provisions of 35 USC §103 and respectfully request withdrawal of the rejection.

Applicant asks that all claims be allowed. Enclosed is a Petition for Extension of Time along with the required fee. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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